Novel Adipose Tissue Targets to Prevent and Treat Atherosclerosis

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Contents

Abstract

Adipose tissue as a major organ of lipid and lipoprotein metabolism has a major impact on metabolic homeostasis and thus influences the development of atherosclerosis and related cardiometabolic diseases. Unhealthy adipose tissue, which is often associated with obesity and systemic insulin resistance, promotes the development of diabetic dyslipidemia and can negatively affect vascular tissue

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A. von Eckardstein, C. J. Binder (eds.), *Prevention and Treatment of Atherosclerosis*, Handbook of Experimental Pharmacology 270, https://doi.org/10.1007/164_2020_363

homeostasis by secreting pro-inflammatory peptides and lipids. Conversely, paracrine and endocrine factors that are released from healthy adipose tissue can preserve metabolic balance and a functional vasculature. In this chapter, we describe adipose tissue types relevant for atherosclerosis and address the question how lipid metabolism as well as regulatory molecules produced in these fat depots can be targeted to counteract atherogenic processes in the vessel wall and improve plasma lipids. We discuss the role of adipose tissues in the action of approved drugs with anti-atherogenic activity. In addition, we present potential novel targets and therapeutic approaches aimed at increasing lipoprotein disposal in adipose tissue, boosting the activity of heat-producing (thermogenic) adipocytes, reducing adipose tissue inflammation, and improving or replacing beneficial hormones released from adipose tissues. Furthermore, we describe the future potential of innovative drug delivery technologies.

Keywords

Adipokines · Atherosclerosis · Brown adipose tissue · Diabetic dyslipidemia · Hyperlipidemia · Inflammation · Insulin resistance · Lipid-lowering therapy · Lipoproteins · Obesity · Perivascular adipose tissue · Thermogenesis · Vascular remodeling · White adipose tissue

1 Introduction

Adipocytes are triglyceride-storing cells present in anatomically distinct adipose tissue depots throughout the mammalian body (Cinti 2001). Originally, two major subtypes, white and brown adipocytes, were identified, both playing an important role in energy metabolism. White adipocytes in white adipose tissue (WAT) store large amounts of triglycerides, typically in a single large lipid droplet, which can be hydrolyzed to provide other organs with free fatty acids (FFA) (Young and Zechner 2013). Brown adipocytes in brown adipose tissue (BAT) also store triglycerides, albeit in lower quantities, and, in many, smaller lipid droplets. When BAT is activated, for example, by exposure to a cold environment, brown adipocytes oxidize fatty acids, glucose, and other fuels in their numerous mitochondria to generate heat (Cannon and Nedergaard 2004). Under chronic cold exposure, adipocytes that are morphologically and functionally very similar to brown adipocytes, referred to as beige adipocytes, develop in WAT depots in a process called WAT browning (Bartelt and Heeren 2014). The number of thermogenic adipocytes thus increases when demand is high. As summarized in Fig. 1, white, brown, and beige adipocytes influence whole-body energy metabolism, lipoprotein levels (Scheja and Heeren 2016), and, through secretion of regulatory molecules, tissue homeostasis in other organs (Scheja and Heeren 2019). How these systemic effects of adipose tissues modulate the development of cardiovascular disease (CVD), and how they can be targeted therapeutically, is the topic of this chapter. Furthermore, local effects exerted by adipocytes found next to blood vessels (perivascular adipocytes) will be described and discussed.

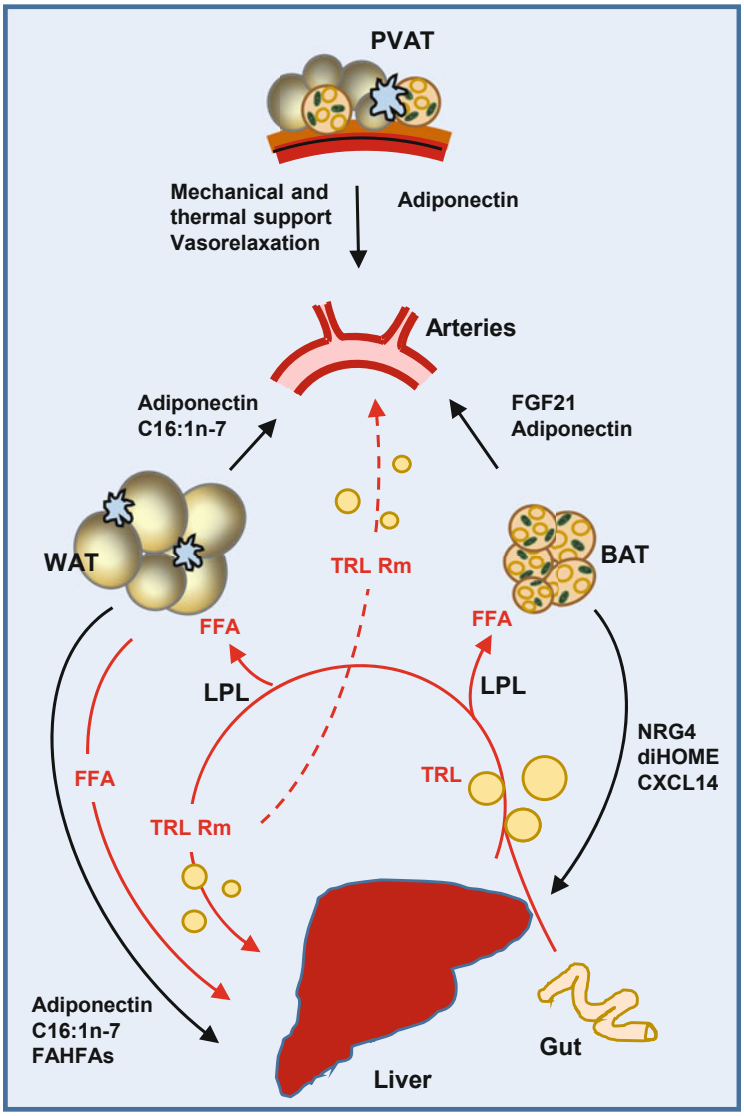

Fig. 1 Role of adipose tissues for cardiometabolic homeostasis under healthy conditions. In metabolic health, white and brown adipose can control systemic lipid homeostasis by regulating both the efficient clearance of triglyceride-rich lipoproteins and the release of fatty acids under catabolic conditions. Healthy adipose tissues harbor mostly anti-inflammatory immune cells (indicated by blue-colored immune cells) that are important to maintain tissue homeostasis. Under this condition, adipocytes mostly release beneficial hormones such as anti-inflammatory lipokines, adiponectin, and FGF21 that support vascular health by direct effects on arteries or indirectly by regulating hepatic lipid metabolism. Overall, healthy adipose tissues are associated with a state of metabolic flexibility that prevents atherosclerosis. *BAT* brown adipose tissue, *FFA* free fatty acids, *FGF21* fibroblast growth factor 21, *LPL* lipoprotein lipase, *NRG4* neuregulin 4, *PVAT* perivascular adipose tissue, *Rm* remnants, *TRL* triglyceride-rich lipoproteins, *WAT* white adipose tissue

2 Types of Adipose Tissue and Their Impact on Cardiovascular Disease

2.1 White Adipose Tissue

The bulk of triglycerides in the body is stored in subcutaneous and intra-abdominal WAT depots. The stored fatty acids can be released from white adipocytes by intracellular triglyceride lipolysis (Young and Zechner 2013). Norepinephrine, which is secreted by sympathetic nerves and signals through β-adrenergic receptors, is the major physiological trigger of lipolysis. β-Adrenergic stimulation elevates cyclic AMP, thereby activating adipose tissue triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL). This regulation ensures that in catabolic states such as fasting or endurance exercise, WAT releases FFA into the circulation to provide other organs with energy. In contrast, after feeding, intracellular lipolysis is suppressed by insulin, and WAT takes up dietary fatty acids from circulating triglyceride-rich lipoproteins (TRL). In this anabolic process, TRL triglycerides are hydrolyzed by lipoprotein lipase (LPL) bound to the luminal side of the capillary endothelium, and the FFA then pass through the endothelium to be taken up and esterified by the adipocytes (Kersten 2014). Apart from their role in fatty acid metabolism, white adipocytes are also an important source of adipokines (adipose peptide hormones) and other secreted regulatory molecules. Notably, only a few of them such as leptin and adiponectin are exclusively expressed in adipose tissue and act at the same time as a true endocrine hormone. In other words, most adipokines are also expressed by cells other than adipocytes and may act predominantly in a paracrine fashion (Scheja and Heeren 2019).

In prolonged periods of caloric surplus, i.e., when energy uptake exceeds energy expenditure, WAT depots expand by increasing adipocyte number (hyperplasia) and adipocyte size (hypertrophy). The resulting overweight or obesity is detrimental when adipocyte hypertrophy prevails (Klöting et al. 2010). In this state of unhealthy obesity, chronic low-grade inflammation occurs in WAT (Crewe et al. 2017), adipocytes become insulin resistant, and fatty acids cannot be stored efficiently any longer. Hence, they are ectopically deposited as part of various lipid species in other organs, a process believed to contribute to the systemic insulin resistance typically associated with obesity (Petersen and Shulman 2018). Another important consequence of limited WAT lipid storage in obesity is liver steatosis. Among other effects, this causes increased secretion of very low-density lipoproteins (VLDL) and thus promotes diabetic dyslipidemia (Scheja and Heeren 2016). Together with pro-inflammatory changes in adipokine patterns, dyslipidemia links expanded WAT depots, especially abdominal visceral fat (Lim and Meigs 2014), to the increased atherosclerosis risk observed in obese individuals (Fig. 2).

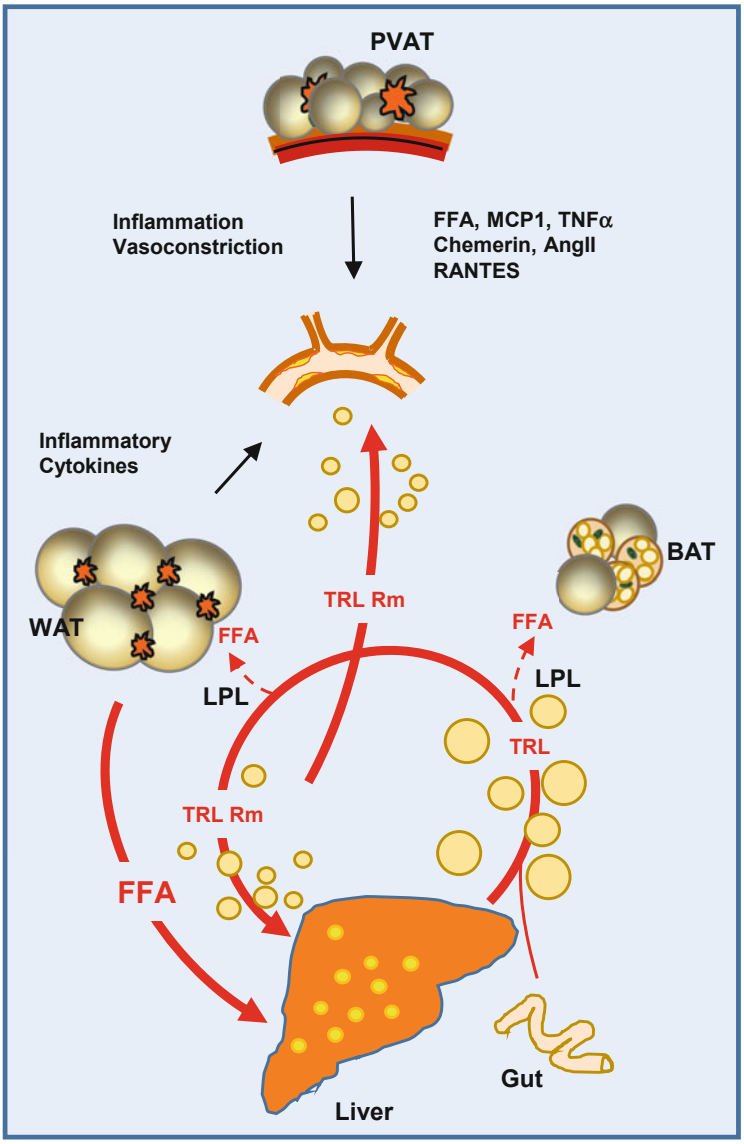

Fig. 2 Hypertrophy and inflammation in adipose tissues cause dyslipidemia and promote atherosclerosis. Chronic caloric surplus and low energy expenditure result in obesity, which is characterized by inflamed (indicated by red-colored immune cells) and hypertrophic adipose tissues as well as dysfunctional brown adipose tissues. Eventually, this causes atherogenic dyslipidemia due to impaired TRL clearance and enhanced fatty acid flux to the liver leading to increased lipoprotein secretion. The lower release of adipocyte-derived anti-inflammatory molecules (see Fig. 1) and pro-inflammatory cytokines in particular those released by PVAT promote inflammation and vasoconstriction. Overall, this creates an immunometabolic state that promotes atherosclerotic plaque formation

2.2 Thermogenic Adipose Tissue

Brown adipocytes present in distinct BAT depots (Zhang et al. 2018) generate heat to maintain body temperature by non-shivering thermogenesis (NST), a process that depends on the mitochondrial proton transporter uncoupling protein-1 (UCP1) that disconnects the respiratory chain from ATP synthesis (Cannon and Nedergaard 2004). NST is triggered by activation of lipolysis through increased β-adrenergic signaling and other catabolic stimuli (Bordicchia et al. 2012). Fatty acids released from the lipid droplets allosterically activate UCP1 and serve as mitochondrial fuel. During prolonged thermogenic stimulation by cold exposure, or other sustained catabolic stimuli such as burn trauma (Sidossis et al. 2015), mitochondria-rich beige adipocytes appear in WAT, a phenomenon called WAT browning (Bartelt and Heeren 2014). Although these adipocytes appear to be developmentally distinct, they are very similar to brown adipocytes with regard to gene expression, morphology, and function. Both brown and beige adipocytes exhibit a very high metabolic capacity and can combust large quantities of triglycerides and other sources of energy when activated. In cold-treated mice, BAT internalizes high amounts of triglycerides from circulating TRL (Bartelt et al. 2011). Under this condition, cholesterol-enriched TRL remnants are efficiently cleared by the liver where bile acid synthesis from cholesterol is increased (Worthmann et al. 2017). Furthermore, the flux of high-density lipoprotein (HDL) cholesterol from the periphery to the liver is enhanced (Bartelt et al. 2017). Consistent with the observed improved lipoprotein profiles, the size of atherosclerotic plaques was reduced in BAT-activated mice fed a cholesterol-rich diet compared to controls (Chang et al. 2012, Berbée et al. 2015). Of note, this beneficial outcome on atherosclerosis depends on lowering of plasma remnant cholesterol, as it was not observed in experiments with mouse models of severely compromised hepatic remnant clearance (LDL receptor (LDLR)- or apolipoprotein (apo) E-deficient mice) where BAT activation and thus TRL processing resulted in elevation of plasma remnant cholesterol (Berbée et al. 2015; Sui et al. 2019). Whether activated BAT or beige WAT has enough metabolic capacity to reduce atherosclerosis in humans needs to be shown. However, a recent, large epidemiological study indicates that high BAT mass inversely correlates with the risk of type 2 diabetes and major cardiometabolic diseases (Becher et al. 2020). Relative to body weight, BAT mass is smaller in humans than in rodents, and it apparently declines in obesity (van Marken Lichtenbelt et al. 2009). However, humans usually live under thermoneutrality, defined as an environmental temperature where the basal metabolic rate generates sufficient heat to maintain body core temperature. When mice are kept under thermoneutral conditions (ca. 30 °C; in dressed humans approximately 24 °C), BAT accumulates lipid and partially loses mitochondria, UCP1, and other determinants of thermogenic capacity (Kotzbeck et al. 2018). Thus, it is likely that in humans, reactivation of BAT and induction of beige WAT, for example, by repeated cold treatments, would profoundly increase metabolic rate and hence the capacity to metabolize atherogenic lipoproteins. Another issue is that metabolic imaging studies to quantify BAT activity in humans are usually done with radioactive glucose analogues. Suitable tracer analogues of

TRL, the major physiological fuel of BAT, still need to be developed. Most adipokines are expressed by both WAT and BAT, and due to its smaller size, BAT is probably less important. However, several adipokines are enriched in thermogenic adipose tissue, and some are induced and released from BAT under thermogenic stimulation or stress conditions (Villarroya et al. 2017). Overall, dysfunctional BAT is likely to influence atherosclerotic development especially by promoting dyslipidemia and inflammation (Fig. 2).

2.3 Perivascular Adipose Tissue

The adventitial layer of arteries is in close contact with adipocytes that form the perivascular adipose tissue (PVAT). PVAT is an important regulator of arterial function. It supports the blood vessel mechanically, by clearing FFA and by releasing paracrine factors that regulate vascular tone, inflammation, redox state, and smooth muscle cell proliferation (Costa et al. 2018). Given these multiple roles, it is not surprising that experimental stripping of arteries in rodents by mechanical or genetic means accelerates the development of atherosclerosis (Chang et al. 2012; Tian et al. 2013; Manka et al. 2014). Perivascular adipocytes may resemble white or brown adipocytes, depending on the anatomical location and the physiological state. For example, PVAT surrounding mesenteric arteries in mice was found to be similar to WAT (Gálvez-Prieto et al. 2008), whereas PVAT associated with the thoracic aorta contains brown-like adipocytes (Fitzgibbons et al. 2011). Of note, the latter adipocytes are functionally thermogenic, as they influence intravascular temperature in mice exposed to cold (Chang et al. 2012).

The quantity of PVAT in humans increases in obesity and is associated with cardiovascular disease (Britton et al. 2012). Mechanistic studies indicate that not only the volume but also altered properties of PVAT in obesity influence the development of atherosclerosis (Costa et al. 2018; Nosalski and Guzik 2017). One important alteration accelerating atheroma formation appears to be increased inflammation and infiltration of macrophages into PVAT (Henrichot et al. 2005; Skiba et al. 2017). Supporting this notion, expression of the pro-inflammatory molecule monocyte chemo-attractant protein-1 in transplanted PVAT is a determinant of neointima formation in a wire injury atherosclerosis model (Manka et al. 2014). Furthermore, PVAT-derived tumor necrosis factor-α is a causal factor for mitochondrial ROS production leading to aortic vasoconstriction in obese mice (Menezes da Costa et al. 2017). Inflammation promotes changes in the secretion of paracrine hormones from PVAT. For example, the release of adiponectin is reduced in obese, diabetic mice, leading to impaired insulin-dependent vasorelaxation (Meijer et al. 2013), whereas expression of the adipokine chemerin in PVAT confers vasoconstriction, and this is linked to obesity-induced hypertension (Ferland et al. 2018; Weng et al. 2017). These and several other hormones secreted by PVAT act as paracrine regulators of vascular tone, hypertension, and atherosclerosis (Nosalski and Guzik 2017) and thereby determine the health of arteries both under homeostatic and inflammatory circumstances (Figs. 1 and 2).

3 Therapies Targeting Adipose Tissue with Proven Clinical Efficacy in the Treatment of Atherosclerosis

3.1 Peroxisome Proliferator-Activated Receptor-γ (PPARγ) Agonists

PPARγ agonists of the thiazolidinedione (TZD) class are insulin-sensitizing drugs used for the treatment of type 2 diabetes. PPARγ is a transcription factor critical for adipocyte differentiation, and WAT and BAT are the tissues with the highest expression. The main target for TZD-based diabetes therapy is dysfunctional hypertrophic adipose tissue where TZDs improve insulin signaling and lipid storage while inducing an anti-inflammatory adipokine profile. Together, these actions lead to less ectopic lipid deposition in liver and muscle and improved systemic insulin sensitivity (Yau et al. 2013). TZDs also have anti-atherogenic activity Saremi et al. 2013; Thorp et al. 2007. Whether these protective cardiovascular effects are mediated by PPARγ expressed in adipocytes, for example, through improved thermogenesis and anti-inflammation (Chang et al. 2018), is unclear as the transcription factor is also expressed and mediates anti-atherosclerotic effects in immune, smooth muscle and endothelial cells (Murakami-Nishida et al. 2019; Subramanian et al. 2010; Qu et al. 2012, Ozasa et al. 2011). Nevertheless, several prospective clinical studies showed an improved plasma lipoprotein profile, reduced carotid artery intima media thickness, fewer cardiovascular disease events, and lower mortality in patients treated with the TZD pioglitazone compared to controls (Hanefeld 2009; Yau et al. 2013, Sartemi et al. 2013). Unfortunately, adverse effects, especially fluid retention, congestive heart failure, and bladder cancer, at least some of them target-related (Yau et al. 2013, Devchand et al. 2018), can offset the desired actions of the drug.

3.2 Niacin

Niacin (nicotinic acid) is a vitamin that, when applied orally at high doses, reduces atherosclerosis and cardiovascular mortality, especially in patients with metabolic syndrome (Superko et al. 2017). One anti-atherosclerotic mechanism of niacin is the improvement of diabetic dyslipidemia, including reduction in triglycerides and small dense LDL as well as the raising of HDL cholesterol (Kühnast et al. 2013). Signaling through the most important niacin receptor HCA2 (GPR109A, HM74) in adipocytes lowers cyclic AMP and reduces lipolysis and, hence, release of FFA. A long-standing hypothesis is that this improves diabetic dyslipidemia, as the decreased FFA flux to the liver entails reduced hepatic VLDL triglyceride secretion (Zeman et al. 2016). This notion has, however, been challenged by a paper describing that in both mice and humans, niacin and synthetic HCA2 ligands acutely lower plasma FFA whereas only niacin reduces plasma triglycerides and LDL cholesterol while elevating HDL (Lauring et al. 2012). Thus, the beneficial effects of niacin on diabetic dyslipidemia are at least in part independent of HCA2-mediated lipolysis. Of note, HCA2 is expressed and mediates anti-inflammatory effects in other artery

wall cell types, in particular macrophages, endothelial cells, and vascular smooth muscle cells (Graff et al. 2016). An important role of macrophages was suggested by a bone marrow transplantation study with LDLR-deficient ($Ldlr^{-/-}$) mice. In this study, niacin was not able to suppress intimal macrophage recruitment and atheroma formation in wild-type acceptor mice that received HCA2-deficient cells, whereas transplantation of HCA2 wild-type hematopoietic cells restored niacin efficacy. This effect was independent of plasma lipid levels (Lukasova et al. 2011). Taken together, niacin has anti-atherogenic properties by improving plasma lipoprotein concentrations especially under diabetic conditions and probably by direct anti-inflammatory effects on immune cells. In addition, niacin may exert anti-atherosclerotic effects through HCA2 by increasing the secretion of adiponectin (Plaisance et al. 2009) and by suppressing pro-inflammatory mediators in adipocytes (Digby et al. 2010).

3.3 Renin-Angiotensin System Blockade

Inhibitors of the renin-angiotensin system (RAS) are widely prescribed drugs for hypertension, known to reduce atherosclerosis in humans and preclinical models, to some degree through their anti-inflammatory activity (Ranjbar et al. 2019). Of note, all components of the RAS are expressed in PVAT (Gálvez-Prieto et al. 2008), and pre-clinical models indicate a role of PVAT RAS in atherosclerosis. For example, angiotensin II was increased in periaortic adipose tissue but not in the circulation or other adipose tissues of $Apoe^{-/-}$ mice with unilateral nephrectomy, a model of accelerated atherosclerosis. Of note, no increase in PVAT inflammatory markers was observed in the nephrectomized mice, and angiotensin receptor blockers (ARBs) reduced atheroma (Kawahito et al. 2013). In another study, aortic transplantation of PVAT from $Apoe^{-/-}$ mice fed a high cholesterol diet increased atherosclerosis in acceptor mice, whereas transplantation of PVAT from angiotensin II type 1 receptor knockout mice or PVAT from ARB-treated mice reduced atheroma (Irie et al. 2015). Taken together, it is plausible that PVAT in part mediates the anti-atherosclerotic efficacy of RAS inhibitors.

4 Novel Therapeutic Targets in Adipose Tissue for Treatment of Atherosclerosis

4.1 Promoting Lipoprotein Disposal and Lipid Storage in Adipose Tissues

WAT is a major site of TRL fatty acid disposal after a meal, and human studies showed that this process is frequently impaired in obese and diabetic subjects (Jacome-Sosa and Parks 2014; Kersten 2014). Improving TRL processing and lipid storage in white adipocytes is, therefore, a suitable approach to reduce plasma triglycerides and hence diabetic dyslipidemia. LPL is the gatekeeper of TRL disposal

in adipose tissue. The activity of the dimeric enzyme is controlled in a complex manner at the level of gene expression, assembly, translocation from adipocytes to the capillary lumen, and interaction of LPL with TRL particles (Kersten 2014). Insulin is the most important positive regulator of LPL activity, whereas angiopoietin-like-4 (ANGPTL4) and APOC3 are prominent negative regulators in adipose tissues (Kersten 2014). APOC3 has attracted a lot of attention in recent years, because plasma concentrations of this abundant apolipoprotein are a major determinant of plasma triglycerides and cardiovascular risk in the human population (Jørgensen et al. 2014; Crosby et al. 2014), explained by APOC3 inhibiting LPL as well as hepatic endocytosis of TRL remnants (Ramms and Gordts 2018; Taskinen et al. 2019). Recently, it became clear that the effect of APOC3 on lipoprotein receptor inactivation seems to be more relevant than its anti-lipolytic action (Gordts et al. 2016), especially as antisense-based reduction of APOC3 substantially lowered triglyceride levels in LPL-deficient patients (Gaudet et al. 2014). In addition to its role in dyslipidemia, APOC3 appears to directly act on arteries and to facilitate subendothelial accumulation of atherogenic particles (Taskinen et al. 2019). Overall, downregulation of APOC3 in the liver efficiently lowers triglycerides, and in part this effect is mediated via TRL disposal in adipose tissue.

ANGPTL4 negatively regulates LPL activity by preventing assembly of LPL and destabilizing the enzyme already during secretion from adipocytes (Dijk et al. 2018). Population-based genetic studies have consistently found reduced plasma triglycerides and reduced coronary artery disease risk in humans with a loss-of-function ANGPTL4 mutation (Bailetti et al. 2018; Stitziel et al. 2016; Dewey et al. 2016). A monoclonal antibody against ANGPTL4 suppressed plasma triglycerides in mice and monkeys (Dewey et al. 2016). Selective knockout of *Angptl4* in brown adipocytes of mice reduced TRL disposal only in BAT (Singh et al. 2018), supporting the notion that targeting ANGPTL4 in adipose tissue can be a means to specifically control organ-specific LPL activity. Importantly, LPL itself is also a drug target. Small molecules that bind to and activate LPL were identified in pharmaceutical screening efforts (Tsutsumi et al. 1993; Geldenhuys et al. 2014).

Another method to increase TRL disposal in adipose tissue is fibroblast growth factor (FGF) 21. FGF21 is an endocrine FGF isoform that fine-tunes systemic glucose and lipid metabolism (Bondurant and Potthoff 2018). At pharmacological doses, it increases insulin sensitivity and lowers blood glucose as well as lipids in mice (Kharitonenkov et al. 2005). Of note, lowering of triglycerides, but not glucose, was the most prominent effect of FGF21 in phase 1b clinical studies (Gaich et al. 2013; Talukdar et al. 2016). Mechanistic studies in mice showed that pharmacologically administered FGF21 acutely lowers plasma triglycerides and FFA. Tracer studies with labeled lipids demonstrated that this was due to higher uptake into WAT and BAT but not into other organs (Schlein et al. 2016). This effect was observed for both TRL-associated and albumin-bound fatty acids, indicating that FGF21 acts at least in part through stimulating fatty acid transport into adipocytes (Schlein et al. 2016).

An alternative target to boost lipoprotein disposal in adipose tissue is C-X-C chemokine motif receptor-7 (CXCR7). CXCR7 is also known as atypical chemokine

receptor-3, because it is not expressed in leukocytes (Berahovich et al. 2010). *Cxcr7*$^{-/-}$ *Apoe*$^{-/-}$ mice on Western-type diet had exacerbated hypercholesterolemia and atherosclerosis, whereas the selective CXCR7 agonist CCX771 attenuated plaque formation in Apoe$^{-/-}$ mice (Li et al. 2014). CCX771 treatment lowered plasma triglycerides and VLDL cholesterol, which could be explained by increased VLDL clearance in visceral WAT but not BAT or other organs. This depot specifically exhibited increased LPL activity and reduced ANGPTL4 (Li et al. 2014).

Taken together, several targets and therapeutic approaches have been identified for the stimulation of lipoprotein clearance in adipose tissue with the aim to lower the plasma levels of atherogenic lipoproteins.

4.2 Boosting Thermogenic Activation

Activated thermogenic adipose tissue takes up energy at a high rate, and, at least in mice, a majority of calories is provided by TRL (Heine et al. 2018). BAT activation was shown to improve diabetic dyslipidemia, to increase reverse cholesterol transport and reduce atherosclerosis in APOE3-Leiden-CETP mice, an atherosclerosis-prone mouse model with humanized lipoprotein metabolism (Berbée et al. 2015; Bartelt et al. 2017). Reduction in atherosclerosis could be achieved by chronic β3-adrenergic receptor (β3-AR) stimulation using a synthetic agonist (Berbée et al. 2015), demonstrating feasibility of pharmacological intervention. Of note, the β3-AR agonist mirabegron, an approved drug for overactive bladder, activates BAT in humans (Cypess et al. 2015), and chronic dosing with mirabegron induces WAT browning (Finlin et al. 2018). β3-AR is highly expressed in adipocytes, and cardiovascular side effects of currently available β3 agonists such as hypertension occur only at high doses and are in part due to cross-reactivity on β1-ARs (Hainer 2016; Loh et al. 2019). Whether chronic BAT activation or induction of beige adipocytes by β3-AR agonists is sufficient to improve diabetic dyslipidemia in humans needs to be shown and is currently under investigation. Importantly, boosting thermogenic adipocytes by β3-AR agonists may counteract atherosclerosis independently of systemic lipoprotein metabolism via local activation of thermogenic adipocytes in PVAT. For example, a recent study demonstrated increased vascular temperature and reduced local inflammation in transgenic mice with higher thermogenic activity in PVAT (Xiong et al. 2017). Given that the common presence of BAT in adult humans has only been recognized recently (Celi 2009), it is likely that drugs directed at thermogenic adipose tissue targets other than β3-AR, such as adenosine A_{2A} agonists (Gnad et al. 2014), will be developed in the future.

4.3 Targeting Inflammation in Adipose Tissue

Chronic, subclinical inflammation is a hallmark of insulin-resistant WAT in unhealthy obesity. Anti-inflammatory interventions in adipose tissue may slow or prevent the development of atherosclerosis by improving lipoprotein disposal,

normalizing systemic glucose homeostasis, and changing the secretome of adipose tissues in a favorable way. General anti-inflammatory therapies can have beneficial cardiovascular effects, as demonstrated by neutralizing antibodies directed against TNFα that reduce cardiovascular events in rheumatoid arthritis patients (Jacobsson et al. 2005) and raise plasma adiponectin levels (Nishida et al. 2008). Although immune cells are not organ-specific and found throughout the body, positive effects of many anti-inflammation therapies are likely to be at least in part mediated via inflammation in adipose tissue. This is especially true for PVAT that is in close proximity with atherosclerosis-prone arteries and exhibits a profound infiltration of macrophages, T-lymphocytes, and other immune cells during initiation and progression of atherosclerosis (Akoumianakis et al. 2017). Many anti-inflammatory proteins can be targeted in PVAT and have the potential to prevent and reduce atherosclerosis, as suggested by rodent studies. For example, the angiotensin 1–7 analogue AVE0991 that signals through the receptor Mas was demonstrated to selectively suppress inflammation in PVAT and reduce atherosclerosis in *Apoe*$^{-/-}$ mice (Skiba et al. 2017). Receptors of the chemokine RANTES (CCL5) are associated with PVAT inflammation, and *Ccl5*$^{-/-}$ mice are protected from perivascular inflammation (Mikolajczyk et al. 2016), while the RANTES receptor antagonist met-RANTES suppresses atherosclerosis in *Ldlr*$^{-/-}$ mice (Veillard et al. 2004). Similarly, CXCL10 signaling regulates T cell infiltration in atherosclerosis, and genetic deficiency of the CXCL10 receptor CXCR3 (Veillard et al. 2005) or treatment with the CXCR3 antagonist NBI-74330 (van Wanrooij et al. 2008) attenuates atherosclerosis in hypercholesterolemic mice. Several other chemokines appear to play an important role in PVAT inflammation and atherosclerosis (Nosalski and Guzik 2017). Taken together, several promising targets to tackle atherosclerosis by reducing inflammation in adipose tissue depots have been identified in mouse experiments. Whether anti-atherosclerotic approaches targeting adipose tissue inflammation with proof of concept in rodents can be translated into human therapies needs, however, to be shown.

4.4 Hormones Derived from Thermogenic Adipose Tissue

Compared to WAT, BAT and other thermogenic fat depots have a small mass and thus are probably a minor source of most circulating adipokines. However, there are exceptions to the rule, and some hormones are enriched in BAT (Villarroya et al. 2017). Recent studies suggest that some of these hormones are potential targets to prevent or treat atherosclerosis. For example, transplantation of BAT into the visceral cavity of *Apoe*$^{-/-}$ mice led to reduction in atherosclerotic plaque size. This was accompanied by increased plasma FGF21 and adiponectin, and the beneficial effect of BAT transplantation in this study could be blocked by β3-AR antagonists (Kikai et al. 2018). Many anti-atherogenic activities of FGF21 have been identified in rodents (Jin et al. 2016; Domouzoglou et al. 2015). Therefore, it is plausible that elevated FGF21 mediates at least some of the effects in this model. Of note, adenosine A_{2A} receptor agonists, molecules that activate thermogenic

adipocytes in mice and humans (Gnad et al. 2014), were found to trigger FGF21 expression and secretion from BAT, and this was important to prevent hypertension-induced cardiac hypertrophy (Ruan et al. 2018). Thus, at least in mice, activated BAT is a meaningful source of cardio-protective and anti-atherosclerotic FGF21.

Moreover, the peptide neuregulin-4 and the linoleic acid derivative 12,13-dihydroxy-9Z-octadecenoic acid (diHOME) have recently been described as hormones enriched in and released by activated thermogenic adipocytes. They act in a paracrine fashion to potentiate thermogenic function and appear to exhibit beneficial metabolic functions in the liver and muscle (Nugroho et al. 2018; Stanford et al. 2018; Pellegrinelli et al. 2018; Guo et al. 2017; Lynes et al. 2017; Wang et al. 2014). It is tempting to speculate that these, and other pro-thermogenic hormones secreted by brown and beige adipocytes such as C-X-C motif chemokine ligand-14 (Cereijo et al. 2018), have a protective effect in atherosclerosis, for example, by increasing lipoprotein disposal or by modulating inflammation.

4.5 De Novo Lipogenesis-Derived Lipokines

Adipose tissue is a quantitatively relevant site of de novo lipogenesis (DNL), the endogenous synthesis of fatty acids from non-lipid precursors. One important feature of unhealthy obesity is increased DNL in the liver accompanied by decreased DNL in WAT (Eissing et al. 2013). Elevated hepatic DNL promotes insulin resistance and is a mechanism that worsens diabetic dyslipidemia by increasing triglyceride availability for VLDL production (Scheja and Heeren 2016). How decreased WAT DNL contributes to the development of metabolic disease has long been elusive. Research of the recent years has provided strong evidence that DNL-associated lipids secreted from adipocytes, coined lipokines, are part of the mechanism. The first lipokine to be identified was the FFA variant of palmitoleate (C16:1n-7), a major fatty acid produced by DNL that was found to be reduced in WAT of obese mice. Palmitoleate FFA turned out to be an anti-inflammatory, insulin-sensitizing molecule that improves systemic glucose homeostasis in mice (Cao et al. 2008). Palmitoleate was identified to reduce atherosclerosis via suppressing pro-inflammatory differentiation of macrophages, and *Apoe*$^{-/-}$ mice on a Western-type diet supplemented with palmitoleate had significantly reduced plaque size compared to control mice (Çimen et al. 2016; Yang et al. 2019). Thus, WAT-derived palmitoleate can reduce atherosclerosis risk by modulating inflammation. It is important to note that WAT-derived palmitoleate is not or only marginally lower in obese, insulin-resistant compared to healthy humans (Eissing et al. 2013; Stefan et al. 2010). Nevertheless, dietary palmitoleate supplementation decreased inflammation and lowered LDL in human subjects (Bueno-Hernández et al. 2017; Bernstein et al. 2014), highlighting the anti-atherosclerosis potential of palmitoleate.

Other lipids proposed as adipose tissue-derived DNL-associated lipokines are fatty acid esters of hydroxy fatty acids (FAHFAs), a novel class of lipids (Yore et al. 2014). WAT levels of certain FAHFA species were shown to depend on DNL. Moreover, circulating levels of DNL-linked FAHFA were shown to be tightly

associated with insulin sensitivity in mice and in humans (Yore et al. 2014; Hammarstedt et al. 2018). In addition, oral FAHFA supplementation was demonstrated to improve glucose tolerance in mice (Yore et al. 2014), an FAHFA effect that has, however, been questioned by another group (Pflimlin et al. 2018). More research is warranted, especially with regard to FAHFA synthesis and degradation as well as FAHFA signaling mechanisms to better understand the role of this novel lipid class in metabolic regulation. Furthermore, studies addressing the association of DNL-derived FAHFAs with cardiovascular risk markers are needed to find out whether FAHFAs modulate the development of cardiovascular disease.

5 Future Directions

In the past decades, many adipokines, chemokines, and other regulatory molecules acting on or derived from adipose tissues that affect the development and progression of atherosclerosis have been identified. One major task will be to successfully translate these findings into the clinics. In some cases such as pioglitazone, cardiovascular clinical benefit is evident; however, adverse effects in other organs have precluded more widespread use or even led to the retraction of the drug. Here, adipose tissue targeted delivery using advanced drug delivery technologies could be a solution. Peptides that selectively bind to endothelium in WAT (Kolonin et al. 2004) and BAT (Azhdarinia et al. 2013), respectively, have been identified, and the WAT-selective peptide was successfully used for WAT-specific drug delivery (Xue et al. 2016). Although this WAT-directed drug delivery system is not suitable for oral application, proof of concept that adipose tissue depots can be targeted specifically was delivered.

Methods to achieve adipose-directed delivery of nucleic acids with the goal to overexpress a beneficial protein, or to modulate endogenous RNA levels, have been considerably advanced in the past years. For example, adipose tissue-directed expression of genes, or suppression using small hairpin RNAs, can be achieved by the means of adeno-associated virus vectors (O'Neill et al. 2014). Another promising approach is the delivery of silencing RNAs encapsulated by glucan shells, a method that specifically delivers the regulatory RNA species to WAT macrophages (Aouadi et al. 2013).

An alternative approach to molecular interventions in unhealthy adipose tissues would be the development of regenerative medicines based on bioelectric stimulation devices to increase the sympathetic tone in specific adipose depots or gene therapy and cell transplantation to restore functional adipocytes. Such innovative concepts and highly advanced technologies would provide a novel therapeutic strategy to target obesity-associated cardiovascular disease.

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